REMARKS

As an initial matter, Applicant and the undersigned wish to thank the Examiner for withdrawing the rejection of Claims under 35 USC §112, second paragraph.

Claims 33-43 are pending in this Application. Claims 33 and 43 have been amended *inter alia* by replacing the plural term "variants" with a singular form "variant" as suggested by the Examiner. In addition, Claims 33 and 43 has been amended as a method for treating a particular clinical condition that is associated with apoptosis.

Claim Objections

Claims 33 and 43 are objected to allegedly because the second occurrence of the term "variant" is improperly recited in the plural form. Claims 33 and 43 have been amended by replacing the plural from with the singular form as suggested by the Examiner, thereby rendering these objections moot.

Double Patenting Rejection

Claims 33-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 7-11, and 34-36 of copending Application No. 10/427,929.

Claims 33-43 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 29-46 of copending Application No. 12/051,373.

Applicant respectfully requests that this issue be deferred until an allowable subject matter is indicated at which time an appropriate Terminal Disclaimer will be filed.

Rejection under 35 U.S.C. §112, first paragraph

Claims 33-43 are rejected under 35 USC §112, first paragraph, allegedly "as containing subject matter which was not described in the specification in such a way as to reasonably convey to **one skilled in the relevant art** that the inventor, at the time the application was filed, had possession of the claimed invention." (emphasis added) See page 4 of the Office Action. In particular, the Office Action alleges that the crux of the rejection under 35 USC §112, first paragraph, is that:

> The specification fails to exemplify or describe the practice of methods of claims 33-43 wherein administering AAT to an intact animal that suffers any of the recited medical conditions **has any affect on the intracellular pathways of apoptosis**, acknowledged in the discussion at pages 3 and 4 of the

> specification, **by inhibiting surface or intracellular proteases to inhibit apoptosis**. The specification proposes no proteases that AAT might affect other than caspases, granzymes, and cathepsins, all of which are intracellular or organelle-resident proteases. **The specification fails to disclose any method of administration of AAT to a subject that delivers AAT to the cytosolic or nuclear compartments of any mammalian cell that may undergo apoptosis in tissues** wherein the medical conditions recited in claim 1 [sic] transpire, e.g., neurons, epithelial cells, muscle cells, or connective tissue cells. The specification does not show that administering AAT may otherwise affect or ameliorate stroke, arthritis, muscular dystrophy, multiple sclerosis, arteriosclerosis, autoimmune disease, ischemia-reperfusion injury, neurodegenerative disease, or myocardial infarction and **establishes no nexus between the ability of AAT to inhibit certain serine proteases and the contribution of serine proteases to these diseases or medical conditions**.

(Emphasis added). See first full paragraph on page 5 of the Office Action.

It is a well established law that when rejecting a claim under the enablement requirement of §112, the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why…the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 27 U.S.P.Q.2d. 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the Examiner must provide evidence or technical reasoning substantiating those doubts. *Id.*; see also, M.P.E.P. §2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 27 U.S.P.Q. 2d at 1513; *In re Marzocchi*, 169 U.S.P.Q. at 369.

The Office Action does not provide any supporting evidence substantiating this alleged nonenablement. The Office Action simply concludes that "The specification fails to disclose any method of administration of AAT to a subject that delivers AAT to the cytosolic or nuclear compartments of any mammalian cell that may undergo apoptosis in tissues...." No evidence is given in the Office Action to show that AAT is not absorbed by the cells. Since the Office Action does provide any evidence supporting nonenablement, the Examiner's conclusory statement doe not meet this initial burden of proof requirement, and therefore the nonenablement rejection is improper.

In the event the Examiner maintains the nonenablement rejection, Applicant provides the following arguments: First, none of the claims require that the apoptosis must occur by the uptake of AAT by cells. By rejecting the claims on the basis that:

> The specification fails to exemplify or describe the practice of methods of claims 33-43 wherein administering AAT to an intact animal that suffers any of the recited medical conditions **has any affect on the intracellular pathways of apoptosis**, acknowledged in the discussion at pages 3 and 4 of the specification, by inhibiting surface or intracellular proteases to inhibit apoptosis.

the Office Action is incorrectly reading the limitations into the claims that apoptosis must occur by affecting the intracellular pathways of apoptosis. Nothing in the claims require inhibiting "intracellular pathways of apoptosis". More significantly, the specification clearly shows AAT inhibits apoptosis and that the disease conditions listed are associated with apoptosis. See, for example, page 4, lines 10-21. It follows then that by inhibiting apoptosis using AAT, these diseases can be treated.

Exhibits A-F

Moreover, attached herewith are Exhibits A-F that show AAT is absorbed by the cells, inhibits apoptosis, and can treat a disease associated with apoptosis.

Exhibit A is a copy of the poster that was presented on October 12-16, 2008 in Montreal. Applicant is the primary investigator for the data used in this presentation. As shown in Exhibit A, AAT is internalized by cells (see, for example, Figure 4 on page 8) and can be used to treat various clinical conditions (see, for example, pages 3 and 9).

Exhibit B is a copy of *Am. J. Pathology*, **2006**, *169*, pp. 1155-1166. As disclosed in Exhibit B, AAT inhibits lung alveolar endothelial cell apoptosis. See for example, the Abstract on page 1155. Furthermore, others have shown AAT can be used to treat "cigarette smoke-induced emphysema in mice". See the paragraph bridging page 1155 and 1156 and reference 11 cited therein.

Exhibit C is a copy of *Am. J. Respir. Crit. Care Med.*, **2006**, *173*, pp 1222-1228. Among other places, the Abstract in Exhibit C discusses that "α_1-antitrypsin may have broader biological effects in the lung, preventing emphysema **through inhibition of alveolar cells apoptosis**." (Emphasis added). See, also, the paragraph bridging the left and the right columns of page 1224 ("Taken together, these results suggest that A1AT inhibits apoptosis in structural lung alveolar cells."); and the paragraph bridging the left and the right columns of page 1225 in the Discussion section ("Our studies support a novel **antiapoptotic function of hA1AT in the lung**, uncoupled from its inhibition of neutrophil-generated serine proteases, and provide the framework for future **studies addressing how A1AT is internalized in alveolar cells and inhibits alveolar structural (noninflammatory) cell apoptosis**.") (Emphasis added). Thus, internalization of AAT by cells and inhibition of apoptosis by AAT is clearly recognized by one skilled in the art.

Exhibit D is a copy of *Circulation*, **2000**, *102*, pp. 1420-1426. Even the title of this article indicates inhibition of apoptosis to treat ischemia/reperfusion injury. Throughout Exhibit

D, authors disclose that AAT inhibits apoptosis and thus can be used to treat ischemia/reperfusion injury. See, for example, Figure 2 on page 1422. ("Treatment with AGP on reperfusion apparently decreased numbers of TUNEL-positive nuclei [i.e., apoptosis] after 24 hours (C), similar to numbers associated with AAT treatment on reperfusion (D)."). See also the left column on page 1422. ("The present study indicates that abrogation of inflammation does not occur when apoptosis inhibitors are administered after 2 hours of reperfusion."). As the Experimental Protocol section discloses, male Swiss mice were used in the experiments. See the left column on page 1421.

Exhibit E is a copy of *Am. J. Respir. Cell Mol. Biol.*, **2003**, *28*, pp. 551-554. This article shows that apoptosis is "a critical element in the pathogenesis of emphysema." See the left column of p. 554. Furthermore, this Exhibit discusses a link between protease/antiprotease imbalance and apoptosis. See, for example, the paragraph bridging pp. 553 and 554. Clearly, Exhibit E supports the finding of the present inventor regarding a connection between the protease activity and apoptosis and ultimately manifestation of clinical conditions.

Exhibit F is a copy of *J. Clin. Invest.*, **2008**, *118*, pp. 394-402. This article also shows a link between apoptosis and emphysema. See, for example, the abstract on p. 394 ("These recent scientific advances support a model whereby … apoptosis … produces the clinically recognized syndrome of emphysema."). More significantly, Exhibit F clearly shows that AAT inhibits apoptosis *in vivo*. See, for example, the left column of p. 397 ("… in a rodent model of emphysema … AAT … inhibit apoptosis…. Since AAT can … and protect against experimental emphysema in rodents…. Indeed, AAT induced the inhibition of caspases, which was associated with reduced oxidant stress in vivo and also in cultured endothelial cells…."). This was recognized by the present inventor as evidenced by the present Application disclosure.

The attached Exhibits confirm what is already disclosed in the present Application. That is, when one skilled in the art administers AAT to a subject, as disclosed in the present Application, one can treat various clinical conditions including those associated with apoptosis.

Moreover, all that the first paragraph of § 112 requires is that the disclosure of a patent application be such that persons skilled in the art, having read the patent application, would be able to practice the inventions described by the claims. There is no legal requirement that this be done in any particular manner; an enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology. *In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971).

Furthermore, a patent application must be deemed to be enabling unless there is reason to doubt the truth of statements contained in the patent application relating to making and using the invention. *Id.,* 169 U.S.P.Q. at 369-370.

Applying this standard clearly renders the present Application enabling and shows that the Applicant had possession of the invention claimed in the pending claims.

It appears the crux of the rejection in the Office Action is that the Applicant has not provided in vivo examples describing that AAT is internalized synthesis of each claimed compound. This fact, however, does not provide any reason to doubt that those skilled in the art having the present patent application before them would be able to practice the claimed inventions.

Many, if not the most, therapeutic use of a compound is first shown by *in vitro* experiments. Given *in vitro* data efficacy, one skilled in the art readily recognizes that such a compound is often applicable *in vivo*. AAT has been used clinically and is readily available; therefore, one skilled in the art having read the present disclosure would readily recognize that Applicant had possession of the claimed invention.

Accordingly, it is submitted that the specification is fully enabling and shows that Applicant had possession of the claimed invention. Therefore, it is respectfully submitted that the rejection under 35 U.S.C. §112, first paragraph, is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants submit that all claims now pending in this Application are in condition for allowance. Therefore, an early Office Action to that effect is earnestly solicited. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at (303) 955-8103.

Respectfully submitted,

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